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Original Article

Impact of endoscopic mucosal resection in patients referred for endoscopic management of Barrett's esophagus

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A B S T R A C T

Background: Barrett's esophagus (BE) may be managed by radiofrequency ablation, endoscopic mucosal resection (EMR), and surgical resection for advanced lesions. The goal of this study was to evaluate the impact of EMR in patients referred for management of BE.

Methods: All patients referred to a tertiary center for management of BE between January 1, 2009 and August 7, 2012 were reviewed and stratified according to dysplasia, Barrett's-related neoplasm, and nodularity. Endpoints included histopathologic characterization of esophageal tissue biopsies and EMR specimens, discrepancy between diagnoses, and subsequent change in management following EMR.

Results: In total, 2648 endoscopies were reviewed. Thirty-five patients having a total of 38 EMRs were included. Mucosal tissue biopsy and EMR specimens were discordant in 24 of 38 specimens (63%). Of these, 20 biopsy results were upstaged (53%) and four downstaged (10.5%) following EMR. The most common change was upstaging to invasive adenocarcinoma. EMR diagnosed 13 cases of invasive carcinoma, 12 of which were upstaged (92%). Based on EMR results, management was changed in 13 cases (34%), primarily to surgery.

Conclusion: Mucosal biopsies and EMR results were discrepant in 63% of cases, with 53% resulting in an upstaged diagnosis. Approximately one-third of these patients had a change in management. In patients referred for BE, EMR was found to be fundamental to accurate grading and should be a component in the evaluation and management of Barrett-related lesions.

Keywords: Barrett's esophagus, Dysplasia, Endoscopic mucosal resection, Radiofrequency ablation

Introduction

In consensus guidelines, radiofrequency ablation (RFA) with or without endoscopic mucosal resection (EMR) is the recommended management for patients with high-grade dysplasia (HGD).[1] Non-dysplastic Barrett's esophagus and carcinoma arising in a background of Barrett's esophagus are often managed with surveillance and surgical resection, respectively. EMR is recommended for patients with Barrett's esophagus with dysplasia with nodules or mucosal irregularity. Many patients are referred for and undergo treatment for Barrett's esophagus and related lesions based on mucosal forceps biopsies, despite studies showing that EMR and biopsy results are frequently discordant.[2–6]

The aim of this study was to evaluate the cohort of patients referred with Barrett's esophagus to determine the impact of EMR on the grading and subsequent management of the disease. We sought to determine the frequency and nature of the discrepancy between the mucosal forceps biopsy results and EMR results in esophageal specimens. The secondary aim was to review the subsequent treatment recommendations to characterize the impact of the EMR on change in management. These results should be of use in understanding the impact and role of EMR in patients referred for endoscopic management of Barrett's esophagus.

Methods

Study design and population

This study was a single-center retrospective cohort study. The study was approved by the Institutional Review Board of Emory University, Atlanta, GA, USA. All patients provided informed consent for esophagogastroduodenoscopy, EMR, endoscopic ultrasound, and/or RFA. The search involved patients receiving esophagogastroduodenoscopy and/or endoscopic ultrasound within the time period from January 1, 2009 to August 7, 2012. The initial search resulted in 1672 patients, who underwent a total of 2648 endoscopic ultrasound and esophagogastroduodenoscopy procedures. This subset was restricted to patients who underwent an

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EMR. Cases involving EMR performed outside of the esophagus and gastroesophageal junction were excluded. Patients without a prior tissue biopsy were excluded. Prior biopsy results were obtained from the study institution or the referring institution. Outside biopsies were not reviewed by the internal institution's pathologists. Internal specimens (biopsy and EMR) were evaluated by two expert pathologists. In the final study set of patients, 38 esophageal and gastroesophageal junction EMRs were performed. The subsequent clinical course for patients following EMR was determined by a review of their medical records. Results were not recorded if an esophageal intervention (such as RFA) occurred between the tissue biopsy and EMR.

Histologic result of the biopsy and EMR was recorded as no evidence of metaplasia, Barrett's esophagus/metaplasia, low-grade dysplasia (LGD), HGD, intramucosal adenocarcinoma (IMC), or invasive adenocarcinoma (INV). LGD was defined as mild architectural complexity with cells having basilar pseudostratified and hyperchromatic nuclei encroaching upon the glands.[7] This set of histologic features is often shared with the diagnosis of "indefinite for dysplasia," in which the specimen has not met all the criteria for a higher-grade classification. They are often combined into one category. In this study, specimens that were indefinite for dysplasia were excluded. If a patient had multiple grades on multiple biopsies, the highest grade was used for that patient. HGD was defined as stratified, hyperchromatic nuclei with nuclear enlargement, and an increased nuclear-to-cytoplasmic ratio, with the presence of prominent nucleoli, increased mitotic figures, and loss of nuclear polarity.[8] IMC was defined as a neoplasm invading into the lamina propria or muscularis muscosa without submucosal invasion. INV was defined as infiltrating neoplastic cells invading the submucosa. Features may include intraluminal necrosis, abortive microglands, or a continuous anastomosing gland pattern.[9] For both biopsy and EMR results, the highest histopathologic grade assigned to a specimen by a reviewing pathologist was considered to be the diagnosis. A downstage was defined when the histologic grade was lower on the EMR specimen than that from the prior biopsy results. An upstage was defined when the EMR results characterized a more advanced histopathologic grade than the prior biopsy result. The location and size of lesion for biopsy and EMR were recorded. Short-segment Barrett's esophagus was defined as an endoscopic length of less than 3 cm, whereas long-segment Barrett's esophagus was 3 cm or greater in length, as measured endoscopically.

Clinical documentation was searched for treatment performed prior to biopsy and EMR and after EMR, to identify all recommendations for changes in management. Patient charts were also reviewed following EMR to determine the management course that was followed.

Results

Study results included data from 38 esophageal EMRs and preceding tissue biopsies from 35 patients. Three patients had two recorded biopsies with a corresponding EMR, whereas the remaining 32 patients had data from only one biopsy and EMR. Patient ages ranged from 28 years to 91 years (mean, 67.06 years; median, 67 years). The ethnicities included Caucasians (28), African Americans (5), and other race patients (2). The results included data from 21 patients with short-segment and 13 patients with long-segment Barrett's esophagus. Reflecting the referral population in a tertiary care setting, 10 of the long-segment disease cases were found to have INV. One patient was not found to have metaplasia on either biopsy or EMR (Table 1). The number of days between the patient's first point of contact at the tertiary center and the last documented point of contact was 440 days.

Table 1 Baseline Demographic Data in the Study Population of Patients Referred for Management of Barrett's Esophagus*

Characteristics	*N* (%)
Gender	
Male	27 (77)
Female	8 (23)
Age (y)	
28–50	3 (9)
51–91	32 (91)
Mean	67
Ethnicity	
Caucasian	28 (80)
African American	5 (14)
Other	2 (6)
Length of metaplasia (cm)	
Short segment	21 (60)
Long segment	13 (37)
No metaplasia	1 (3)

* Data from 35 patients that participated in this review.

Histologic characteristics of the mucosal biopsy and subsequent EMR are compared in Table 2. The EMR histologic data yielded the following diagnoses: three with no metaplasia, eight with Barrett's esophagus/metaplasia, one with LGD, five with HGD, eight with IMC, and 13 with INV. The tissue biopsy and EMR results were discordant in 24 of 38 specimens (63%). Of the biopsy results, 20 were upstaged (53%) and four were downstaged (10.5%) following EMR (Table 2). In the remaining 14 (37%) cases, the biopsy and EMR results were similar. In cases of discrepancy, EMR diagnosed IMC or INV most commonly. Biopsy diagnosed eight cases showing no metaplasia. These biopsies were taken from patients with a high suspicion of Barrett's esophagus and those who were being monitored after a previous diagnosis of Barrett's esophagus or carcinoma. These specimens were collected at the same time as the EMR specimens. Of these eight lesions, five (63%) were upstaged and three (37%) were concordant with EMR. Biopsy identified seven cases of nondysplastic Barrett's esophagus, with one (14%) being upstaged by EMR and six (86%) being concordant with EMR. The one low-grade lesion diagnosed by tissue biopsy was upstaged by EMR. Biopsy identified 10 high-grade lesions, of which six (60%) were upstaged and two (20%) were downstaged by EMR, and two (20%) were concordant with EMR. Tissue biopsy identified 11 IMC lesions, with seven (64%) being upstaged and two (18%) downstaged by EMR, and two (18%) being concordant with EMR. Tissue biopsy diagnosed one lesion as INV, which was concordant with EMR.

EMR detected more cases of IMC and INV than biopsy. Eight cases of IMC were identified, with six (75%) being upstaged from biopsy results and two (25%) being concordant with biopsy. Two of the upstaged lesions were diagnosed as no metaplasia on biopsy, showing major discordance with EMR. EMR diagnosed 13 cases of

Table 2 Histopathologic Results of Biopsy Specimens Comparing Initial Forceps Biopsy and Subsequent Endoscopic Mucosal Resection Characterizations

Tissue biopsy result	EMR Result						Total
	No metaplasia	Metaplasia	LGD	HGD	IMC	INV	
Suspicious	3	1	0	1	2	1	8
IM	0	6	0	0	0	1	7
LGD	0	0	0	0	1	0	1
HGD	0	1	1	2	3	3	10
IMC	0	0	0	2	2	7	11
INV	0	0	0	0	0	1	1
Total	3	8	1	5	8	13	38

HGD, high-grade dysplasia; IM, intestinal metaplasia; IMC, intramucosal adenocarcinoma; INV, invasive adenocarcinoma; LGD, low-grade dysplasia; Suspicious, suspicious for intestinal metaplasia.

INV, 12 of which were upstaged from biopsy (92%) and the remaining one was concordant (8%). One of these preceding biopsies showed no metaplasia and another showed nondysplastic Barrett's esophagus, indicating major discordance with EMR. Fourteen patients were found to have esophageal nodules on endoscopy, six with Barrett's esophagus, one with LGD, two with HGD, three with IMC, and two with INV.

In the 38 sets of specimens, 13 changes were made in the management after diagnoses by EMR (34%; Table 3). RFA was performed in 10 cases after EMR pathology results showed dysplasia. Two patients were referred for cryoablation and 10 were referred for surgery. All the cryoablation and surgery referrals followed an EMR diagnosis of INV. Patients with INV undergoing ablative therapy were not candidates for surgery due to comorbid conditions. RFA was performed in a total of 26 of the 35 patients (74.29%).

Discussion

The recommended management for patients with Barrett's esophagus with HGD without carcinoma is RFA with or without EMR. EMR may be a better tool for the histopathologic characterization of disease in patients with Barrett's esophagus, and we sought to determine the impact of EMR on a cohort of patients referred for Barrett's esophagus management. There was a higher proportion of neoplastic lesions and IMC reflecting the subset referred to a tertiary care center for management. The study demonstrated that mucosal forceps biopsies and EMR results were discrepant in 63% of cases, with 53% resulting in an upstaged diagnosis. In contrast to recommendations, these data do not suggest that EMR should be an optional component in management. Rather, EMR was fundamental to the accurate histopathologic characterization of Barrett's esophagus-related lesions and resulted in a change in management in approximately one-third of the patients in the tertiary referral cohort.

Supporting these findings, studies have also shown that EMR is a better diagnostic tool than mucosal biopsy for patients with Barrett's esophagus without nodules. Changes in diagnosis between tissue biopsy and EMR have demonstrated rates varying from 20% to 49%.[5,9–11] The present study shows a higher degree of discordance between specimens (in 63%). Many discrepancies were found between biopsy and EMR results, with the former showing HGD and IMC whereas the latter revealed intramucosal and invasive cancer. In the present study, six of 10 HGD lesions were upstaged: three to IMC and three to INV. Similarly, seven of 11 lesions diagnosed as intramucosal by biopsy were found to be invasive by EMR. Findings suggesting cancer prompt a referral for surgical consultation. The lesions that were upstaged to invasive cancer after EMR corresponded to the largest and arguably the most important discrepancy between biopsy and EMR results. Management was changed for 12 of 13 patients in that group (92.31%), with a referral for evaluation of esophagectomy. Two patients were not considered to be surgical candidates despite the diagnosis and received salvage cryoablation. One of the 13 management changes occurred when a patient with HGD on biopsy was found to have nondysplastic Barrett's esophagus on EMR. This patient was monitored with serial endoscopy and medical therapy instead of RFA.

Table 3 Changes in Management of Patients with Discrepant Results from Prior Tissue Forceps Biopsy and Subsequent Endoscopic Mucosal Resection

Biopsy result	EMR result	Recommendation following EMR (*N*)*
HGD	BE	Intensive surveillance (1)
Suspicious for metaplasia	INV	Esophagectomy (1)
BE	INV	Esophagectomy (1)
HGD	INV	Esophagectomy (2), cryoablation (1)
IMC	INV	Esophagectomy (6), cryoablation (1)

BE, Barrett's esophagus; HGD, high-grade dysplasia; IMC, intramucosal adenocarcinoma; INV, invasive adenocarcinoma.

* This column demonstrates the recommendation following the final diagnosis based on the EMR specimen.

From a treatment standpoint, EMR may also be useful. A large study described data from October 1996 to September 2002 of 279 patients with HGD or IMC undergoing EMR. Patients with invasive carcinoma were not involved due to the possibility of lymph node metastases. They had extensive follow-up at 1 month, 2 months, 3 months, 6, and 9 months after treatment and then at 6-month intervals for another 5 years. The eradication rate for these patients was 94.5%. The rate of metachronous lesions requiring further endoscopic intervention was 21.5%. Three of these patients underwent surgery.[12] In another study with 37 patients undergoing stepwise EMR for HGD or early neoplasia, 89% had complete eradication with 2% that experienced complications (asymptomatic perforation and delayed bleeding).[13] EMR has a clear role in the treatment of dysplastic lesions and may potentially have a role in the treatment of superficial or intramucosal lesions in select subsets of patients.

Of the 14 nodules resected by EMR, the histologic characterization was six nondysplastic Barrett's lesions, two low-grade dysplastic lesions, two high-grade dysplastic lesions, three IMCs, and one invasive carcinoma. Thus, in this setting, Barrett's nodules had a high likelihood of advanced histology (57%). In a 2001 study, the presence of a nodule was found to increase the likelihood of submucosal invasion.[14] However, nodules have also been identified in overdiagnosis of esophageal neoplasia.[15] Our data indicate that EMR of Barrett's nodules results in a high frequency of dysplastic and malignant histopathologic characterizations, and that EMR is the modality of choice for the management of nodules and irregular mucosa. Long-segment disease was found to be associated with more advanced histology, reflecting the most commonly affected subset of the population[16,17]; most patients involved in the study were Caucasian males (34; 89.47%).

This study had a number of limitations. Although the design was retrospective, it permitted observation of the change in management based on the EMR results. The sample size was moderate at 35 and reflected a highly selected subset of patients referred to a tertiary care institution. The rate of advanced histology was much higher in this cohort than would be expected in a typical Barrett's cohort. Nevertheless, examination of this referral cohort provided a larger proportion of patients with advanced histology from which a change in management could be examined. Biopsies performed at outside institutions were not over-read by pathologists at the study institution, as the goal was to characterize the change in management that occurred following EMR. The baseline state was that established by the prior forceps biopsy and the revised state was that established following histopathologic examination of the specimen generated by EMR. If the patient had not been referred, management would presumably have proceeded based on the forceps biopsy result.

Until the revised publication of treatment recommendations in 2008, the recommended management for Barrett's esophagus with HGD was surgical resection. With the relatively recent introduction of RFA and the excellent outcomes with endoscopic management of Barrett's esophagus, the recommended management for LGD, HGD, and IMC is changing. It may be possible to eliminate LGD in 91% of patients and eliminate HGD in 81% of patients using RFA.[18] Some studies suggest that EMR may be an effective treatment modality for IMC,[9,11,12] and may especially be suited to the large cohort of patients who are not surgical candidates. INV is in most cases best managed with surgical resection. Thus, accurate characterization of the pretreatment histology has become the critical determinant of divergent treatment recommendations. In our study, EMR changed the pathologic characterization in 63% of cases, and patients would

have been erroneously classified if forceps biopsies alone had been used to guide management. These data suggest that EMR may be less an optional component in the management of Barrett's esophagus and more a key determinant in the accurate characterization of patients' baseline histology.

Conflicts of interest

I have no conflicts of interest.

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